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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,697	10/05/2006	Jurgen Wagner	33714-US-PCT	2925

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
WEBB, WALTER E	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,697	WAGNER ET AL.	
	Examiner	Art Unit	
	WALTER E. WEBB	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 10/29/2008, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of transplant rejection or graft-versus-host disease, does not reasonably provide enablement for prevention of graft-versus-host disease.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the

claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to prevention of graft-versus-host disease. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not

the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Jacobsohn et al. (Bone Marrow Transplantation 2001). Jacobsoohn et al. discusses complications of diagnosing graft-versus-host disease (GVHD) and also gives an idea of the breadth of this disease. For example, they note that the disease covers more than just complication of the skin, gastrointestinal tract and liver. It can affect almost any organ in the body, and it often mimics autoimmune diseases such as Sjörgren's syndrome, rheumatoid arthritis, systemic lupus erythematosis and scleroderma (see pg. 1047, left column, 2nd paragraph). The reference teaches unpredictability in the treatment of GVHD insofar as potent immunosuppressive agents increase the risk of opportunistic infection, which can lead to significant morbidity (see pg. 1047, right column, 2nd paragraph). The reference also shows that the risk of GVHD exists even after a patient has been diagnosed has having inactive GVHD, since seven patients of the inactive GVHD group developed active GVHD (see pg. 1049, left column, paragraphs 2-5).

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prevention", the term will be interpreted expansively. The term "prevention" may vary widely in meaning, from "preventing" a disease from occurring to "preventing" it from progressing. Nor is the term limited by any time frame.

"experimentation".

The claims are thus very broad insofar as they suggest that one will not experience the disease when taking the claimed agent; that should one get the disease, it will not worsen; or that following its treatment, it will not recur. While such "prevention" might theoretically be possible under strictly controlled laboratory conditions, as a practical matter it is nearly impossible to achieve in the "real world" in which patients live.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for prevention of graft-versus-host disease. Applicant provides an *in vivo* Graft v. Host Model, where spleen cells from Wistar/F rats are injected into the right hind footpad of hybrid rats. The results showed inhibition of lymph node enlargement in 60 to 80% of the rats when compound A was administered. These results support unpredictability since 20 to 40% of the rats developed enlarged lymph nodes. Still, there is no evidence or reasonable basis to conclude that the disease would not eventually develop in the rats. Furthermore, there is no evidence to suggest that these results can be extrapolated to other types of grafts.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to prevent graft-versus-host disease as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103--New

Claims 5 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heath et al. (US 5,545,636) in view of Albert et al., (US 2004/0053949), and further in view of Goekjian et al., (Expert Opinion Investigative Drugs 2001).

Applicant argues that there is no motivation to choose the components from Heath and Albert that are necessary to achieve the instant methods. Applicant argues that neither Heath nor Albert indicates which PKC isozymes are associated with the transplant rejection or GVHD and without this indication one of skill in the art would not use the compound of Heath to treat these diseases. However, this does not mean that the artisan avoid using the compounds of Heath to treat transplant rejection or graft-versus-host disease. Addressing the issue of obviousness, the Supreme Court emphasized that "[a] person of ordinary skill is… a person of ordinary creativity, not an

automaton." KSR v. Teleflex, 127 S.Ct. 1727, 1742 (2007). Heath teaches that its compounds are isozyme selective inhibitors of beta-1 and beta-2 isozymes of PKC. Graft-versus-host disease (GVHD) is recognized in the prior art as a PKC-linked immunodisorder.[2] Goekjian et al. teaches the use of a compound with selective inhibition for beta-1 and beta-2 isozymes of PKC, Ro 31-0432, for treating graft-versus-host response models in rats (see Goekjian et al. at pg. 2131, left column, 2nd paragraph; see also Table 4, at pg. 2128 for relation to isozymses of PKC). Ro 31-0432 has also been compared to indolocarbozoles, which are of the same class as the compounds of Heath and Albert (see Goekjian et al., section 3.3, at pg 2131).

Since the prior art has shown that compounds with the same isozyme selectivity for PKC are useful for treating GVHD, the artisan would have reasonably concluded that the compounds of Heath would be useful in treating GVHD as well, especially since other indolocarbozoles have been recognized as being useful for treating GVHD, as evidenced by Albert.

[2] Hong Hu, "Recent discovery and development of selective protein kinase C inhibitors." Drug Discovery Today 1996:1(10); at pg 445, right column, 1st paragraph.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Walter E. Webb whose telephone number is (571) 270-3287. The examiner can normally be reached on 8:00am-4:00pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Walter E. Webb
/Walter E Webb/
Examiner, Art Unit 1612

/Frederick Krass/

Supervisory Patent Examiner, Art Unit 1612